

AD _____

GRANT NUMBER DAMD17-96-1-6248

TITLE: Mutations in ATM, Radiation Exposure and Breast Cancer
Risk Among Black and White Women

PRINCIPAL INVESTIGATOR: Elizabeth L. Schubert, Ph.D.

CONTRACTING ORGANIZATION: University of Washington
Seattle, Washington 98195-7720

REPORT DATE: August 1998

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for public release;
distribution unlimited

The views, opinions and/or findings contained in this report are those of the author(s) and should not be construed as an official Department of the Army position, policy or decision unless so designated by other documentation.

DTIC QUALITY INSPECTED 4

REPORT DOCUMENTATION PAGE			Form Approved OMB No. 0704-0188	
Public reporting burden for this collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington, VA 22202-4302, and to the Office of Management and Budget, Paperwork Reduction Project (0704-0188), Washington, DC 20503.				
1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE August 1998	3. REPORT TYPE AND DATES COVERED Annual (1 Aug 97 - 31 Jul 98)		
4. TITLE AND SUBTITLE Mutations in ATM, Radiation Exposure and Breast Cancer Risk Among Black and White Women		5. FUNDING NUMBERS DAMD17-96-1-6248		
6. AUTHOR(S) Elizabeth L. Schubert, Ph.D.				
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) University of Washington Seattle, Washington 98195-7720		8. PERFORMING ORGANIZATION REPORT NUMBER		
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012		10. SPONSORING / MONITORING AGENCY REPORT NUMBER		
11. SUPPLEMENTARY NOTES		19981118 040		
12a. DISTRIBUTION / AVAILABILITY STATEMENT Approved for public release; distribution unlimited		12b. DISTRIBUTION CODE		
13. ABSTRACT (Maximum 200 words) In some families, predisposition to breast cancer is inherited as a genetic trait. Thus far, a few highly penetrant genes responsible for inherited breast cancer have been identified. An important and unresolved question of breast cancer etiology is whether there are other genes which have a more moderate effect on breast cancer risk, possibly involving more women than do other inherited mutations. It has been suggested that mutations in the Ataxia-Telangiectasia gene (ATM) and cellular damage such as radiation exposure could be involved with breast cancer in this manner. In order to address this question, we are screening a population-based series of African-American and Caucasian breast cancer patients and controls as well as a series of patients with particular phenotypes for mutations in the ATM gene. This study will detect potential mutations in the ATM gene which confer breast cancer risk.				
14. SUBJECT TERMS Breast Cancer ATM, African-American and Causasian, mutation, genetics		15. NUMBER OF PAGES 14		
		16. PRICE CODE		
17. SECURITY CLASSIFICATION OF REPORT Unclassified	18. SECURITY CLASSIFICATION OF THIS PAGE Unclassified	19. SECURITY CLASSIFICATION OF ABSTRACT Unclassified	20. LIMITATION OF ABSTRACT Unlimited	

FOREWORD

Opinions, interpretations, conclusions and recommendations are those of the author and are not necessarily endorsed by the U.S. Army.

ES Where copyrighted material is quoted, permission has been obtained to use such material.

ES Where material from documents designated for limited distribution is quoted, permission has been obtained to use the material.

ES Citations of commercial organizations and trade names in this report do not constitute an official Department of Army endorsement or approval of the products or services of these organizations.

ES ^{NA} In conducting research using animals, the investigator(s) adhered to the "Guide for the Care and Use of Laboratory Animals," prepared by the Committee on Care and Use of Laboratory Animals of the Institute of Laboratory Resources, National Research Council (NIH Publication No. 86-23, Revised 1985).

ES For the protection of human subjects, the investigator(s) adhered to policies of applicable Federal Law 45 CFR 46.

ES In conducting research utilizing recombinant DNA technology, the investigator(s) adhered to current guidelines promulgated by the National Institutes of Health.

ES In the conduct of research utilizing recombinant DNA, the investigator(s) adhered to the NIH Guidelines for Research Involving Recombinant DNA Molecules.

ES In the conduct of research involving hazardous organisms, the investigator(s) adhered to the CDC-NIH Guide for Biosafety in Microbiological and Biomedical Laboratories.


 8/26/98
PI - Signature Date

Table of Contents
Postdoctoral Fellowship Annual Report
August 1998
Elizabeth L. Schubert, Ph.D.
Grant DAMD17-96-1-6248

Front Cover	page 1
Standard Form 298	page 2
Foreword	page 3
Table of Contents	page 4
Introduction	page 5
Body of Report	pages 6-8
Table 1	page 9
Table 2	page 10
Conclusions	page 11
References	pages 12-14

Introduction

Breast cancer predisposition is inherited in an autosomal dominant manner in some individuals (Newman et al 1988). Currently, the inheritance of breast cancer predisposition is clearly associated with a few highly penetrant genes, most notably BRCA1 and BRCA2, in rare families (reviewed in Szabo and King 1995). In our experience with families who exhibit a high risk for inherited predisposition to cancer (families with at least four cases of breast or ovarian cancer), we estimate that approximately 20% are unresolved after screening for mutations in the BRCA1 and BRCA2 genes (Schubert et al 1997). This indicates that other, as yet unidentified, genes exist which are involved in breast cancer predisposition. Some of these currently unidentified genes may convey only a moderately increased risk of breast cancer, potentially with disease expression among mutation carriers dependent on specific environmental exposures. Such variably penetrant genetic predisposition could account for a greater population risk of breast cancer than the relatively rare highly penetrant gene mutations, although it would convey less risk to individual heterozygotes. One gene that has been suggested to play a role in moderately increased risk of breast cancer is the gene mutated in Ataxia-Telangiectasia (ATM). This study seeks to clarify the role of ATM in breast cancer predisposition. Specifically, this study asks whether ATM heterozygotes are predisposed to breast cancer.

Ataxia-Telangiectasia (AT) is a recessive genetic disorder (reviewed in Lavin and Shiloh, 1997) characterized by progressive cerebellar ataxia, blood vessel lesions (telangiectasias) and immunodeficiencies. Patients affected with AT are prone to develop lymphoma and leukemia and are extremely sensitive to ionizing radiation. Various regions of ATM have been identified as specific functional domains, including a carboxy-terminal protein kinase domain (Savitsky et al 1995a, Savitsky et al 1995b). The ATM gene product has been shown to play an important role in cellular response to DNA damage, particularly that from ionizing radiation, as a component of a cell-cycle checkpoint pathway (reviewed in Hoekstra 1997). All AT patients identified to date have inherited two germ-line mutations at the ATM locus and most mutations identified truncate the ATM protein. Multiple mutations in ATM have been discovered in AT patients worldwide (The Ataxia-Telangiectasia Mutation Database), with some founder effects of particular mutations in certain populations (Stankovic et al 1998, Telatar et al 1998, Chessa et al 1997, Gilad et al 1996). Most AT patients have the classically identified severe disease phenotype, however some studies have found evidence of particular ATM mutations which are associated with variant phenotypes (Stankovic et al 1998, Gilad et al 1998, Bar-Shira et al 1997, McConville et al 1996).

Epidemiological studies of the families of children suffering from AT have shown an increased incidence of cancer, particularly breast cancer, in the relatives of such patients (Athma et al 1996, Easton 1994, Pippard et al 1988, Swift et al 1987). Family studies have also suggested that exposure to ionizing radiation increases cancer risk in ATM heterozygotes (Swift et al 1991), which is a compelling idea, particularly given the sensitivity of AT patients to radiation and the known function of the ATM gene product in cellular response to DNA damage. The focus of our study has been to investigate this question by examining breast cancer patients, both at a population level as well as those who have a phenotype that indicates possible involvement of ATM such as previous ionizing radiation exposure or an extreme response to such radiation, for ATM heterozygosity. Such a breast cancer patient-based approach complements the studies of AT families which have already been reported.

Body of Report

This study is based on the hypothesis that ATM heterozygotes have an increased susceptibility to breast cancer, particularly when exposed over the course of a lifetime to cellular damage such as ionizing radiation. We originally proposed to screen a large, population-based series of breast cancer patients completely for alterations in the ATM gene. However, more recent reports that ATM heterozygosity is not found in a large number of breast cancer patients (Chen et al 1998, FitzGerald et al 1997, Vorechovsky et al 1996a, Vorechovsky et al 1996b) and reports of founder mutations in ATM with differing effects (and therefore potentially differing cancer risks; (Stankovic et al 1998, Telatar et al 1998) have lead us to redirect our efforts in a more focused manner than was originally proposed. The studies of Vorechovsky et al, FitzGerald et al and Chen et al examined series of breast cancer patients for ATM gene mutations without finding a significant number of mutations. We feel that these results are important but not definitive; it may be that ATM mutations overall are not common in the general breast cancer population but that some founder mutations are frequent in some populations. Alternatively, it may be that ATM mutations are more prevalent in particular sub-populations of patients who have undergone triggering environmental exposure and who may have distinct cancer phenotypes. Studies indicate the possibility of particular ATM mutations which lead to distinct sub-phenotypes (Gilad et al 1998, Bar-Shira et al 1997, Taylor et al 1997, McConville et al 1996), leaving open the possibility that breast cancer susceptibility is one such sub-phenotype arising from particular ATM mutation(s). Evidence for such breast cancer predisposing ATM alleles is found in the recent report of Stankovic et al (1998), which describes a founder mutation in Great Britain that may lead to a greater susceptibility to breast cancer due to its particular effects on the ATM protein. This British mutation is also interesting as the increased risk of cancer is associated with a less severe AT phenotype, possibly due to the particular functional domain of the gene which is affected. It may be that individuals with particular breast cancer predisposing ATM alleles also have a distinct cancer phenotype, potentially involving environmental triggers to induce disease. We have therefore altered the focus of our study to examine patients at a population level for such founder mutations as well as to completely screen the gene in a targeted group of breast cancer patients with specific environmental exposures and/or phenotypes.

Given the information outlined above, which was not available at the time of writing our original proposal, we have changed the focus of our ATM screening in breast cancer patients. The population of patients that we are now screening for ATM mutations reflects a redefinition of our original hypothesis, which is that ATM heterozygotes with breast cancer may have particular cancer predisposing mutations or exhibit a particular cancer phenotype. We have therefore grouped our study into two parts; the targeted screening of specific portions of the gene encompassing known founder mutations that could predispose to breast cancer at a significant population level in a population-based set of breast cancer patients and controls, and the complete screening of ATM in a selected group of patients with particular environmental exposures or phenotypes which we believe, based on the known biology of ATM, are the most probable to be associated with ATM mutations.

For the targeted screening of particular mutations in a population-based series of breast cancer patients, we have analyzed by single-strand confirmation analysis (SSCA) the 17 regions of ATM with the highest number of founder mutations, based on the Ataxia-Telangiectasia Mutation Database, in 141 patient samples. These targeted regions of ATM encompass 28% of the coding sequence, but contain 43% of all protein truncating ATM mutations and all of the founder mutations reported to date (see Table 1). The patient samples being used in this portion of the study are part of the Carolina Breast Cancer Study (CBCS), a population-based study of both African-American and Caucasian women diagnosed above and below the age of 50 (Newman et al 1995). CBCS samples are sent to us as anonymously coded DNA samples and the University of Washington Institutional Review Board has approved our use of them in this study. The CBCS samples are ideal for examining the question of ATM in breast cancer susceptibility as extensive clinical and environmental exposure information, including radiation exposure, is already recorded from each participant. Records from any patient who is found to have a mutation in ATM would

therefore be able to be examined for unusual environmental exposures or clinical phenotype. Tumor blocks are also available from most CBCS patients for LOH analysis in any patient who was shown to have an ATM mutation. The series of 141 CBCS breast cancer patients being screened for ATM mutations includes 60 African-American and 81 Caucasian women, evenly distributed in age at diagnosis above and below the age of 50. To the best of our knowledge, this series of African-American breast cancer patients is the most extensively studied for ATM mutations to date. In the case of a SSCA variant being detected in the initial patient screen, we also analyzed that segment of ATM in a set of 138 CBCS controls (63 African-American and 85 Caucasian women) which were ascertained to match the patients as closely as possible in age. As not all segments of ATM had positive results in the initial SSCA screen, we analyzed 13 regions of ATM in the controls as well as the patients. The SSCA analysis of the CBCS samples is currently three-quarters complete in the cases and controls combined, with all ATM regions being analyzed at least once. Results of the SSCA and variant sequencing to date are in Table 2. If any particular ATM mutation is detected in significant numbers in CBCS patients, it will be the preliminary data needed to expand the set of patients screened to determine the population prevalence of the mutation and estimate its effects to the general US patient population.

The second group of breast cancer patients included in our ATM analysis is that of patients with a distinct phenotype that we believe indicates possible ATM involvement in their cancer based on the known biology of ATM. These patients were selected from the following groups: previous radiation exposure, radiation sensitivity, families with at least 3 cancer cases and the common inheritance of a single ATM allele between affected members, or a breast cancer patient who has had a child with AT. Samples from patients in this targeted series were initially screened by SSCA in the selected regions outlined above (see Table 1 and Table 2), and now are being completely screened for ATM mutations through the entire coding sequence by the protein truncation assay (PTT; Telatar et al 1998). The PTT assay has the advantage that it is a cDNA based assay that detects splicing variants as well as protein-truncating mutations. Any positive results from this study will be the preliminary data needed to expand the screening series to more patients from an appropriate subgroup.

The specific patients currently being screened for mutations in ATM are: 8 breast cancer patients who exhibited a severe sensitivity to radiation therapy for their cancer, 5 families with at least 3 cancer cases and the common inheritance of a single ATM allele between affected family members, 2 patients who had received radiation therapy for Hodgkin's Lymphoma before being diagnosed with breast cancer, and one set of parents of an AT child. The 5 families included in this study include 3 families with 3 cases of breast cancer, one family with 2 cases of breast and 2 cases of ovarian cancer, and one family with 1 breast, 2 ovarian, 2 colon and 5 prostate cancer cases. This range of cancer types is consistent with those seen in AT families (Morrell et al 1990). Previous BRCA1 and BRCA2 mutation testing in these families was negative. The mother of the AT child reports that she stood next to her son during his radiation therapy for cancer and that her breast subsequently affected with cancer was within the field of this radiation exposure. Her husband was included in this series as a positive control for ATM mutation detection, as the father of an AT child he is an obligate heterozygote. In the aggregate, we believe that screening this series of patients will indicate which phenotype is associated with ATM mutations and if there is evidence for particular ATM allele(s) which cause a particular susceptibility to breast cancer. The series of radiation sensitive breast cancer patients is particularly interesting, given previous data regarding the radiation sensitivity of cells taken from AT heterozygote patients (West et al 1995, Thacker 1994) and the role of ATM in cellular response to radiation (reviewed in Hoekstra 1997). Two recent reports have examined similarly radiation-sensitive breast cancer patients for ATM mutations with negative results (Appleby et al 1997, Ramsay et al 1998), however the sum total of patients screened in the two studies was 31, and therefore our 8 patients will significantly increase the total number of such patients examined for ATM mutations to date. All patients were enrolled in the study after appropriate informed consent within the structure of our University of Washington Institutional Review Board for Human Subjects agreement.

Since the original submission of this grant, the complete cDNA sequence, genomic organization, and genomic sequence of ATM have been published (Savitsky et al 1995b, Uziel et al

1996, Platzer et al 1997), eliminating the need to obtain this information from other sources. Our preliminary screening strategy for this set of patients has been targeted screening by single-strand conformational analysis (SSCA) of genomic DNA for protein truncating ATM mutations with known genomic causes reported multiple times (Table 1). Many of the mutations identified in ATM to date are deletions in cDNA for which the genomic basis is unclear, such variants were disregarded in this targeted screen as they have the potential to be artifacts. The polymerase chain reaction (PCR) primers used in this SSCA analysis were those of Vorechovsky et al (1996a). Fragments screened to date include 2581 nucleotides of the 9168 nucleotides of the ATM coding region (Savitsky et al 1995b). This encompasses 43% of the ATM coding region and the adjoining mRNA splicing regions of the exons examined. Results from the initial screen are described in Table 2.

Future plans are to expand our patient series as warranted from initial results. If there is evidence for ATM mutations in a particular group of breast cancer patients (such as the radiation sensitive patients) or for particular ATM mutation(s) present in the CBCS breast cancer patients, then we will expand the study to include more patients from the relevant group. For example, if we find evidence for ATM mutations in the radiation sensitive breast cancer patients, we will expand our ATM screening to more such patients. With positive preliminary data on ATM mutations in a particular subset of patients, we would be able to embark on collaborations with our clinical colleagues to obtain more such patient samples. Alternatively, if there is evidence for a particular ATM mutation which predisposes to breast cancer, we will expand our screen for that ATM mutation in more breast cancer patients. Functional analysis of any ATM mutation would also be carried out, as discussed in the original proposal. LOH at the ATM locus in tumors from patients with ATM mutations is also planned, as discussed in the original proposal. We have already obtained tumor samples from the families involved in this study, other samples will be available as needed.

Table 1: Regions of ATM with Common Protein Truncating Mutations
(The ATM Mutation Database, July 6 1998 update)

<u>Region</u>	<u>Number of individual mutations reported</u>	<u>Total number of mutations reported</u>
exon 12	6	11
exon 15	2	2
exon 16	2	4
exon 20	2	5
exon 24	3	3
exon 39	3	3
intron 40	1	3
exon 43	4	5
exon 46	5	8
exon 51	3	5
exon 52	2	2
exon 53	1	7
exon 54	3	10
exon 55	6	10
exon 58	3	6
exon 63	4	5
exon 64	4	4
17 fragments	54 individual mutations	93 total mutations

The sum total of truncating mutations reported in these genomic regions is 93, or 43% of a total number of 216 truncating mutations reported in the ATM Mutation Database. These regions encompass 2581 bp of the ATM coding sequence, or 28% of the entire 9168 bp.

Table 2: Data from SSCA analysis of selected genomic regions of ATM

A. CBCS Patients

Region	Times the same variant was detected (by race)	Sequencing results ¹
exon 12	8 (6 African-American / 2 Caucasian)	1236-3 T _N polymorphism
exon 12	1 (African-American)	incomplete
exon 15	1 (African-American)	2096 A>G (Glu>Gly) ²
exon 16	1 (Caucasian)	2125+22 A>C
exon 39	1 (Caucasian)	5558 A>T (silent) ²
exon 39	1 (African-American)	incomplete
exon 43	6 (3 African-American / 3 Caucasian)	6025 T>G (Tyr>Asp) ^{2,3}
exon 46	1 (African-American)	incomplete
exon 52	1 (African-American)	incomplete
exon 53	3 (1 African-American / 2 Caucasian)	incomplete
exon 54	2 (1 African-American / 1 Caucasian)	incomplete
exon 58	1 (Caucasian)	incomplete
exon 63	10 (7 African-American / 3 Caucasian)	8847 A>T (silent) ^{2,3}

B. CBCS Controls⁴

Region	Times the same variant was detected (by race)	Sequencing results ¹
exon 12	5 (3 African-American / 2 Caucasian)	incomplete
exon 15	2 (Caucasian)	incomplete
exon 16	1 (Caucasian)	incomplete
exon 20	1 (African-American)	incomplete
exon 39	1 (Caucasian)	5558 A>T (silent) ²
exon 39	2 (Caucasian)	incomplete
exon 43	1 (African-American)	incomplete
exon 52	1 (Caucasian)	incomplete
exon 53	1 (Caucasian)	incomplete
exon 63	3 (2 African-American / 1 Caucasian)	incomplete

C. Non-CBCS patients (selected by phenotype)

Region	Times the same variant was detected (phenotype)	Sequencing results ¹
exon 12	3 (Radiation sensitive)	1544 G>A (Ser>Asn) ^{2,3}
exon 12	1 (AT heterozygote)	1591 G>C (Ala>Pro) ^{2,3}
exon 39	7 (radiation sensitive, AT heterozygote, family)	incomplete
exon 55	1 (family; does not segregate with disease)	incomplete
exon 63	1 (family; does not segregate with disease)	8847 A>T (silent) ^{2,3}
exon 64	1 (family; does not segregate with disease)	incomplete

¹ Numbers given are based on the ATM cDNA, nt 1 is the start of translation. Sequencing of variants is still underway and is not complete in all cases.

² Previously unreported variant (Ataxia-Telangiectasia Mutation Database)

³ Unconfirmed variant; resequencing is underway to confirm initial sequence results

⁴ CBCS controls were not analyzed in regions where no variants were detected in patients

Conclusions

This study is still in progress, however after significant screening we have not yet uncovered a truncating ATM mutation in any breast cancer patient. The variants that we have identified to date have all been silent or missense variants, and do not clearly result in loss of function of the ATM protein. Final results of the CBCS population portion of this study will indicate if any variant is seen in significantly higher numbers in breast cancer cases than in controls. Final results in the selected patient portion of this study will indicate if ATM mutations predispose to particular cancer phenotypes. It is premature at this time to make final conclusions, but data so far indicates that protein truncating ATM mutations are not extremely common in breast cancer patients from the groups analyzed in this study.

References

Appleby JM, Barber JBP, Levine E, Varley JM, Taylor AMR, Stankovic T, Heighway J, Warren C, Scott D (1998) Absence of mutations in the ATM gene in breast cancer patients with severe responses to radiotherapy. *Br J Cancer* 76(12):1546-1549

The Ataxia-Telangiectasia Mutation Database: <http://www.vmmc.org/vmrc/atm.htm>

Athma P, Rappaport R, Swift M (1996) Molecular genotyping shows that Ataxia-Telangiectasia heterozygotes are predisposed to breast cancer. *Cancer Genet Cytogenet* 92:130-134

Bar-Shira A, Gilad S, Khosravi R, Russell P, Chessa L, Jorgensen TJ, Shiloh Y (1997) Genotype-phenotype variants in A-T and A-T variants. "Ataxia-Telangiectasia and ATM: Functional, Genetic and Clinical Ramifications", A-T Children's Project scientific meeting, Baltimore MD, August 1997.

Chen J, Birkholtz GG, Lindblom P, Rubio C, Lindblom A (1998) The role of Ataxia-Telangiectasia heterozygotes in familial breast cancer. *Cancer Res* 58:1376-1379

Chessa L, Prudente S, Piane M, Russo G, Negrini M (1997) The repertoire of the ATM gene mutations in Italy. "Ataxia-Telangiectasia and ATM: Functional, Genetic and Clinical Ramifications", A-T Children's Project scientific meeting, Baltimore MD, August 1997.

Easton DF (1994) Cancer risks in A-T heterozygotes. *Int J Radiat Biol* 66(6):S177-S182

FitzGerald MG, Bean JM, Hegde SR, Unsal H, MacDonald DJ, Harkin DP, Finkelstein DM, Isslbacher KJ, Haber DA (1997) Heterozygous ATM mutations do not contribute to early onset of breast cancer. *Nat Gen* 15:307-310

Ford D, Easton DF, Bishop DT, Narod SA, Goldgar DE and the Breast Cancer Linkage Consortium (1994) Risks of cancer in BRCA1-mutation carriers. *Lancet* 343: 692-695

Gilad S, Khosravi R, Shkedy D, Uziel T, Ziv Y, Savitsky K, Rotman G, Smith S, Chessa L, Jorgensen TJ, Harnik R, Frydman M, Sanal O, Portnoi S, Goldwicz Z, Jaspers NGJ, Gatti RA, Lenoir G, Lavin MF, Tatsumi K, Wegner RD, Shiloh Y, Bar-Shira A (1995) Predominance of null mutations in Ataxia-Telangiectasia. *Hum Mol Genet* 5:433-439

Gilad S, Bar-Shira A, Harnik R, Shkedy D, Ziv Y, Khosravi R, Brown K, Vanagaite L, Xu G, Frydman M, Lavin MF, Hill D, Tagle DA, Shiloh Y (1996) Ataxia-Telangiectasia: founder effect among North African Jews. *Hum Mol Gen* 5:2033-2037

Gilad S, Chessa L, Khosravi R, Russell P, Galanty Y, Piane M, Gatti RA, Jorgensen TJ, Shiloh Y, Bar-Shira A (1998) Genotype-Phenotype relationships in Ataxia-Telangiectasia and variants. *Am J Hum Genet* 62:551-561

Hoekstra MF (1997) Responses to DNA damage and regulation of cell cycle checkpoints by the ATM protein kinase family. *Curr Opin Gen Dev* 7:170-175

Lavin MF and Shiloh Y (1997) The genetic defect in Ataxia-Telangiectasia. *Annu Rev Immunol* 15:177-202

McConville CM, Stankovic T, Byrd PJ, McGuire GM, Yao Q-Y, Lennox GG, Taylor AMR (1996) Mutations associated with variant phenotypes in Ataxia-Telangiectasia. *Am J Hum Genet* 59:320-330

- Morrell D, Chase CL, Swift M (1990) Cancers in 44 families with Ataxia-Telangiectasia. *Cancer Genet Cytogenet* 50:119-123
- Newman B, Austin MA, Lee M, King M-C (1988) Inheritance of human breast cancer: Evidence for autosomal dominant transmission in high-risk families. *Proc Natl Acad Sci USA* 85: 33044-33048
- Newman B, Moorman PG, Milikan R, Qaqish BF, Geradts J, Aldrich TE, Liu ET (1995) The Carolina Breast Cancer Study: Integrating population-based epidemiology and molecular biology. *Br Ca Res Treat* 35:51-60
- Pippard EC, Hall AJ, Barker DJP, Bridges BA (1988) Cancer in homozygotes and heterozygotes of Ataxia-Telangiectasia and Xeroderma Pigmentosum in Britain. *Ca Res* 48:2929-2932
- Platzer M, Rotman G, Bauer D, Uziel T, Savitsky K, Bar-Shira A, Gilad S, Shiloh Y, Rosenthal A (1997) Ataxia-Telangiectasia locus: sequence analysis of 184 kb of human genomic DNA containing the entire ATM gene. *Genome Res* 7:592-605
- Ramsay J, Birrell G, Lavin M (1998) Testing for mutations of the Ataxia-Telangiectasia gene in radiosensitive breast cancer patients. *Radiother Oncol* 47:125-128
- Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S, Ashkenazi M, Pecker I, Frydman M, Harnik R, Patanjali SR, Simmons A, Clines GA, Satiel A, Gatti RA, Chessa L, Snal O, Lavin MF, Jaspers NGJ, Taylor AMR, Arlett M, Miki T, Weissman SM, Lovett M, Collins FS, Shiloh Y (1995) A single ataxia telangiectasia gene with a product similar to a PI-3 kinase. *Science* 268:1749-1753
- Savitsky K, Sfez S, Tagle DA, Ziv Y, Satiel A, Collins FS, Shiloh Y, Rotman G (1995b) The complete sequence of the coding region of the ATM gene reveals similarity to cell cycle regulators in different species. *Hum Mol Gen* 4:2025-2032
- Schubert EL, Lee MK, Mefford MC, Argonza RH, Morrow JE, Hull J, Dann JL, King M-C (1997) BRCA2 in American families with four or more cases of breast or ovarian cancer: recurrent and novel mutations, variable expression, penetrance, and the possibility of families whose cancer is not attributable to BRCA1 or BRCA2. *Am J Hum Gen* 5:1031-1040
- Stankovic T, Kidd AMJ, Sutcliffe A, McGuire GM, Robinson P, Weber P, Bedenham T, Bradwell AR, Easton DF, Lennox GG, Haites N, Byrd PJ, Taylor AMR (1998) ATM mutation and phenotypes in Ataxia-Telangiectasia families in the British Isles: expression of mutant ATM and the risk of leukemia, lymphoma and breast cancer. *Am J Hum Genet* 62:334-345
- Swift M, Reitnauer PJ, Morrell D, Chase CL (1987) Breast and other cancers in families with Ataxia-Telangiectasia. *N Engl J Med* 316:1298-1294
- Swift M, Morrell D, Massey RB, Chase CL (1991) Incidence of cancer in 161 families affected by Ataxia-Telangiectasia. *N Engl J Med* 325:1831-1836
- Szabo CI and King M-C (1995) Inherited breast and ovarian cancer. *Hum Mol Genet* 4:1811-1817
- Taylor AMR, Stankovic T, Kidd AMJ, Sutcliffe A, McGuire GM, Robinson P, Weber P, Bedenham T, Easton DF, Lennox GG, Haites N, Byrd PJ (1997) ATM mutations and phenotypes in A-T families in the British Isles; expression of mutant ATM and the risk of leukaemia,

lymphoma and breast cancer. "Ataxia-Telangiectasia and ATM: Functional, Genetic and Clinical Ramifications", A-T Children's Project scientific meeting, Baltimore MD, August 1997.

Telatar M, Teraoka S, Wang Z, Chun HH, Liang T, Castallvi-Bel S, Udar N, Borresen-Dale A-L, Chessa L, Bernatowska-Matuszkiewicz E, Porras O, Watanabe W, Junker A, Concannon P, Gatti RA (1998) Ataxia-Telangiectasia: Identification and detection of founder-effect mutations in the ATM gene in ethnic populations. *Am J Hum Genet* 62:86-97

Thacker J (1994) Cellular radiosensitivity in Ataxia-Telangiectasia. In *J Rad Biol* 66: 587-596

Uziel T, Savitsky K, Platzer M, Ziv Y, Helbitz T, Nehls M, Boehm T, Rosenthal A, Shiloh Y, Rotman G (1996) Genomic organization of the ATM gene. *Genomics* 33:317-320

Vorechovsky I, Rasio D, Luo L, Momaco C, Hammarstrom L, Webster ADB, Zaloudik J, Barbanti-Brodano G, James M, Russo G, Croce CM, Negrini M (1996a) The ATM gene and susceptibility to breast cancer: analysis of 38 breast tumors reveals no evidence for mutation. *Ca Res* 56:2726-2732

Vorechovsky I, Luo L, Lindblom A, Negrini M, Webster DB, Croce CM, Hammarstrom L (1996b) ATM mutations in cancer families. *Ca Res* 56:4130-4133

Vorechovsky I, Luo L, Dyer MJS, Catovsky D, Amlot PL, Yaxley JC, Foroni L, Hammarstrom L, Webster AB, Yuille MAR. (1997) Clustering of missense mutation in the Ataxia-Telangiectasia gene in sporadic T-cell leukaemia. *Nat Genet* 17: 96-99

West C, Elyan S, Berry P, Cowan R, Scott D. A comparison of the radiosensitivity of lymphocytes from normal donors, cancer patients, individuals with Ataxia-Telangiectasia (A-T) and A-T heterozygotes. *Int J Rad Biol* 68:197-203